IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

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| SHEILA E. SCHRANK,<br><br>*on behalf of himself*<br>*and all others similarly situated;*<br><br>Plaintiff<br><br>v.<br><br>SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE<br><br>Defendant. | Case No. 07-cv-4965-CMR<br>CIVIL ACTION<br><br>**JURY DEMAND REQUESTED** |

**AMENDED CLASS ACTION COMPLAINT**

## CLASS ACTION COMPLAINT

Plaintiff Sheila E. Schrank ("Plaintiff"), on behalf of himself and all others similarly situated, allege the following against Defendant GlaxoSmithKline ("Defendant" or "GSK"), based upon personal knowledge where applicable, information and belief and the investigation and research of counsel:

## NATURE OF THE ACTION

1. Plaintiff and the Classes are all consumers who have been prescribed and purchased or paid for part or all of the purchase price of the prescription drugs Avandia® (generically referred to as rosiglitazone maleate), Avandamet® (a combination of rosiglitazone maleate and metformin) and Avandaryl® (a combination of rosiglitazone maleate and glimepiride) (collectively, "Avandia" or "the Avandia drugs").

2. Avandia is one of two thiazolidinediones ("TZD" or glitazones) approved by the Food and Drug Administration ("FDA") on May 25, 1999 as an oral antidiabetic agent which acts primarily by increasing cell insulin sensitivity. TZDs lower the blood sugar levels of persons with diabetes. Avandia is recommended and prescribed for the management of Type II diabetes mellitus, also known as non-insulin-dependent diabetes mellitus ("NIDDM") or adult-onset diabetes. Millions of individuals in the United States have used Avandia to treat their Type II diabetes.

3. GSK has promoted the idea that the lowering of blood sugar levels demonstrates that Avandia enhances the transport of sugar from the blood to cells thereby improving cell health and the overall health of the patient. Thus, GSK claims

that blood sugar level control is a valid "surrogate", which reflects the broader efficacy of Avandia.[1] Unfortunately, in this instance, GSK's surrogate is an extremely poor indicator that Avandia provides a health benefit.

4. Although Avandia lowers blood sugar levels, it does not enhance the health of persons with diabetes. The drug actually *increases one's chance of heart attack by over 40%. See* Psaty B, Editorial: "The Record on Rosiglitazone and the Risk of Myocardial Infarction." *New England Journal of Medicine* 357:15 July 2007: 67-69 (emphasis added).

5. Avandia users can also develop coronary artery disease ("CAD"), macular edema, bone fractures in women, and/or liver failure. Hence, while use of Avandia may lower the blood sugar levels of a person with diabetes, it does so at great risks.

6. According to a February 25, 2010 report from The Institute for Safe Medication Practices, more than 1,000 reports of patient deaths associated with Avandia were received for the first three quarters of 2009, more than any other drug monitored.

7. GSK has concealed, and continues to conceal these very real risks which have been known to GSK since at least 1999, when Avandia was approved for sale.

8. To increase the sales of Avandia, Defendant embarked on a comprehensive and carefully-orchestrated scheme to promote Avandia's safety, efficacy and effectiveness through a fraudulent and deceptive marketing program. Plaintiff and

[1] P. Gaede, et al. "Lowering of blood sugar levels has not, in itself, been proven to provide a health benefit for persons with diabetes." "Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes." *New England Journal of Medicine* February 7, 2008; and "For Safety, NHLBI Changes Intensive Blood Sugar Treatment Strategy in Clinical Trial of Diabetes and Cardiovascular Disease." *National Institutes of Health* press release regarding ACCORD trial dated February 6, 2008.

the Classes were among the principal victims of Defendant's wrongful scheme to promote and market the Avandia drugs.

9. Defendant (a) deliberately misrepresented the scientific, medical and clinical data concerning the safety, efficacy, effectiveness, and superiority of Avandia over comparable drugs; (b) suppressed or mischaracterized negative studies of the drug; and (c) caused false and misleading presentations to be made to physicians and those paying for Avandia – including consumers such as Plaintiff – concerning Avandia's safety, efficacy and effectiveness and lack of purported side effects.

10. In June 2007, prompted by studies of Avandia that showed an increasing risk of heart attacks and heart-related disease from the drug, the House Committee on Oversight and Government Relations held a hearing to examine how the FDA had assessed the safety of Avandia. It was revealed that a senior FDA scientist had recommended a black box warning for Avandia as early as February 2006, but the FDA allegedly removed that scientist from work on Avandia because she voiced concerns about the safety of the drug.

11. Similarly, after another extensive review of Defendant's internal documents, senior Senate members, on Februrary 18, 2010, concluded that Defendant was aware of the possible cardiac risks associated with Avandia years before the evidence became public; Defendant had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner; Defendant intimidated independent physicians and strategized ways to minimize findings that Avandia may increase cardiovascular risk; and Defendant schemed to downplay findings that alternative drugs might reduce cardiovascular risk.

12. Thus, although Defendant had longstanding knowledge of the dangers associated with Avandia, including significant heart attack or heart-disease related risks, Defendant has engaged, and continues to engage, in a nationwide, uniform marketing campaign involving misstatements of Avandia's safety, efficacy and effectiveness and deliberately concealed these dangers in order to promote its drug.

13. Further, Defendant concealed and failed to properly and adequately disclose adverse events to Plaintiff and the Classes.

14. Defendant also misrepresented, and continues to misrepresent, Avandia's safety, efficacy, effectiveness and superiority over older medications, including sulfonylureas and metformin, to the healthcare community, consumers, third-party payors, and others, with the dual goals of increasing sales and market share of Avandia and, thus, increaseing GSK's profits.

15. The financial success of Defendant's scheme depended upon targeting consumers like Plaintiff, third-party payors insurers and health providers. Avandia was a much more expensive medication (approximately twenty-two times as expensive) than older, available drugs that were in often more effective, and more tolerable than Avandia. The average monthly prescription cost for older diabetes drugs like metformin varied from $4 to $100. The cost for Avandia varied from $90 to $220.

16. The cost of Avandia has an enormous impact on consumers, including these Plaintiff and the Classes.

17. Many insured patients, like Plaintiff, have some element of cost-sharing in their prescription benefit with third-party payors. Third-party payors place drugs like Avandia on formularies (a master list of pharmaceutical drugs, and the amount of money

reimbursable for each drug based on the price negotiated with the manufacturer, and the type of insurance program the insured patient has paid for). In many cases, the cost of the drug corresponds with the amount that a plan participant must contribute as a co-payment – the generic drugs require a lower co-payment while preferred brand name drugs require a higher co-payment. In these cases, the rise in co-payment for consumers merely mirrored the rise in the overall cost of brand-name drugs such as Avandia. In other cost-sharing prescription plans, members of the Class pay a flat co-payment for Avandia (regardless of the price).

18. There are also members of the Class, uninsured or insured, who paid the full price for Avandia.

19. Thus, Defendant set out to persuade Plaintiff and the healthcare community, including third-party payors to favor Avandia over alternative treatments that were cheaper, safer and/or more efficacious than Avandia.[2] Plaintiff paid for Avandia in quantities far exceeding its warranted use, and these payments (and resulting revenues for Defendant) were the direct result of GSK's fraudulent scheme.

20. From the time of their releases until approximately May of 2007, the Avandia drugs proved to be blockbusters for Defendant. More than 6,000,000 people worldwide have taken these drugs to control blood sugar since the first Avandia drug came on the market in 1999. Since its introduction, Avandia has been used on a regular basis by at least one million individuals in the United States.

21. Defendant's unlawful scheme to inflate sales of Avandia was extraordinarily successful, with U.S. sales soaring to approximately $1.8 billion in 2005

[2] Drug manufacturers also attempt to keep harmful drugs on formularies by "bundling" the harmful drug with other drugs which locks in customers, increase drug prices, and increase profits.

and approximately $2.36 billion in 2006. Even in 2007, when serious health risks were revealed concerning Avandia, sales only declined to approximately to approximately $1.55 billion. Even now, in 2009, sales for Avandia topped $658 million, making it a hugely successful drug for GSK.

22. This is a proposed New York statewide class action on behalf of the "Refund Class" or those who have been prescribed and/or purchased, reimbursed and/or paid for part or all of the purchase price of Avandia drugs nationwide and alleges violations of New York General Business Law § 349.

23. Plaintiff seeks recovery for their payments for Avandia and the amounts by which Defendant was unjustly enriched on behalf of a New York State class.

24. GSK's conduct, as described herein, caused the Plaintiff's injuries and damages because Plaintiff and the Refund Class paid for the higher cost of these drugs, including co-payments, and were deprived lower cost alternative treatments. Plaintiff and the Refund Class were required to pay more for Avandia than other cheaper alternative treatments available on their respective health plans because of Defendant's deceptive schemes. Based on the misinformation disseminated by Defendant in making their decision to pay for Avandia, Plaintiff and the Refund Class have been directly harmed by their economic loss, an injury that is unaffected by whether any given patient who ingested Avandia suffered adverse side effects.

25. Plaintiff also seeks medical monitoring (defined below) on behalf of the "New York Medical Monitoring Class" or members residing in New York State based on their increased risk of disease from their exposure to Avandia. Defendant's conduct caused each New York Medical Monitoring Class member to have an increased risk of

contracting a serious latent disease.

26. The medical monitoring Plaintiff and New York Medical Monitoring Class seek: 1) to create a reasonable and necessary court-supervised medical testing/monitoring program for the pathologic conditions associated with Avandia use both in the past and future and 2) a court-supervised fund for Plaintiff and the New York Medical Monitoring Class for the reimbursement of out-of-pocket expenses associated with reasonable and necessary testing/monitoring for pathologic conditions associated with Avandia use, both in the past and future.

27. Plaintiff and the New York Medical Monitoring Class seek to represent Avandia users who have not suffered Avandia-related personal injuries including: cardiac ischemia, coronary artery disease (CAD), and myocardial infarction (MI)), but who are at a heightened risk of developing cardiovascular ailments as a result of their exposure to Avandia.

28. Plaintiff and the New York Medical Monitoring Class can be categorized as "High Risk" for future myocardial ischemic events based upon the duration of their exposure to Avandia; to wit, those with at least twelve weeks of exposure to Avandia are "High Risk" for cardiovascular events as a result of its defects.

29. Plaintiff and the New York Medical Monitoring Class deemed "High Risk" for future myocardial ischemic events would seek reasonable and necessary testing/monitoring for pathologic conditions associated with Avandia use.

30. Through early detection, the success of aggressive treatment and prevention of serious cardiac events increases exponentially. Medical monitoring will give Plaintiff and the New York Medical Monitoring Class an opportunity to survive the

harm that Defendant inflicted on them.

## PARTIES

31. Plaintiff Sheila Schrank is a resident of Great Neck, New York who was prescribed and purchased Avandia for Type II diabetes on or after May 25, 1999.

32. Upon learning about the risks associated with Avandia, Plaintiff Schrank stopped taking Avandia and has not had any of the medical monitoring requested herein. Plaintiff Schrank was exposed to Avandia for at least twelve weeks and has been injured as a result of the unlawful conduct alleged herein.

33. Defendant GlaxoSmithKline is a Pennsylvania corporation with its principal place of business at One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania. GlaxoSmithKline was formed in 2001 through the merger of Glaxo Wellcome and SmithKline Beecham. As the surviving entity of this merger, GSK is liable for the actions and inactions of the prior companies. GSK designs, produces, markets and promotes Avandia, Avandamet and Avandaryl in New Jersey and nationwide. GSK has manufacturing sites in Pittsburgh, Pennsylvania, Clifton, New Jersey and Parsippany, New Jersey. At all relevant times, GSK acted by and through its agents, servants, workers, employees, officers and directors, all of whom were acting through the course and scope of their actual and apparent authority, agency, duties or employment.

## JURISDICTION AND VENUE

34. This Court has subject matter jurisdiction over this action pursuant to the Class Action Fairness Act of 2005, 28 U.S.C. § 1332(d)(2) because Plaintiff and Refund

Class members are of diverse citizenship from Defendant; there are more than 100 class members; and the aggregate amount in controversy exceeds $5,000,000.

35. This Court has personal jurisdiction over the parties because Defendant is a resident or has agents and representatives in this State. Defendant is authorized to do business and in fact does business in this state, and Defendant has sufficient minimum contacts with this state and otherwise intentionally avails itself of the markets in this state through the distribution, promotion, marketing and sale of its products in this state, to render the exercise of jurisdiction by this Court permissible under traditional notions of fair play and substantial justice. The Avandia related marketing and sales directives eminated from Defendant's headquarters in Pennsylania and Defendants designed and distributed their research studies from its home office here.

36. Venue is proper in this District under 28 U.S.C. § 1391. The claims asserted in this Complaint arise, in part, within this District. A subsantial part of the events and conduct giving rise to the violations of law complained of herein occurred or emanated from this District. Defendant resides in the State. Defendant also conducts business with consumers in this District and has caused injury to residents in this state.

37. Finally, the class action lawsuit referenced in the caption above has been transferred to this Court as per the Transfer Order of the Judicial Panel on Multi-District Litigation dated November 13, 2007. Plaintiff in the transferred action reserves his/her rights of remand to the districts from which he/she was transferred at or before conclusion of the pre-trial proceedings.

## FACTUAL ALLEGATIONS

### A. FDA Regulations for Marketing and Promotion in the United States

38. Pursuant to the Federal Food, Drug and Cosmetic Act ("FDCA"), new pharmaceutical drugs may not be marketed in the United States until FDA determines that the drug is "safe for use" and effective for all "conditions prescribed, recommended, or suggested" on a drug's label. *See* 21 C.F.R. 99.103; *see also* 21 C.F.R. §201.5.

39. The indications and dosages approved by the FDA are set forth in the drug's labeling, the content of which is also approved by the FDA.

40. A manufacturer's, a statement that a drug is "effective" or "works" or "has been proven to . . ." is understood to mean that well-controlled clinical studies support the use. To make such a statement without such clinical trial proof is misleading. Further, failure to inform physicians that no placebo-controlled clinical trials support a representation of drug efficacy is a violation of a pharmaceutical company's obligation to disclose the necessary information. *See*, 21 C.F.R. § 99.205.

41. In any other circumstance, a manufacturer cannot disseminate information of a drug to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or federal and state government agencies unless such information is fair and balanced and the manufacturer meets the following conditions:

- The information concerns a drug that has been approved, licensed and cleared for marketing by the FDA;
- The information is in the form of an unabridged copy of a peer-reviewed scientific or medical journal article or reprint, or an unabridged reference publication that pertains to a clinical investigation involving the drug and that is considered scientifically sound by experts who are qualified to evaluate the product's safety or effectiveness;
- The information does not pose a significant risk to the public health;
- The information is not false or misleading; and

- The information is not derived from clinical research conducted by another manufacturer, unless permission is received from that manufacturer.

*See*, 21 C.F.R. § 201.6(a); *see also*, 21 U.S.C. §§ 360aaa; 360aaa-1.

42. With regard to the second practice – manufacturer's involvement in CME programs – the FDA's examination of these practices led to the publication of an agency enforcement policy in 1997 entitled, "Guidance for Industry: Industry-Supported Scientific and Educational Activities." 62 Fed. Reg. 64,074, 64,093, 1997 WL 740420 (F.R.) (1997). This guidance document states that CME programs must be truly *independent* of the drug companies, and sets forth a number of factors that the FDA will consider in determining whether a program is "free from the supporting company's influence and bias." *Id.*

43. Sections 502(a) and 201(n) of the FDCA (21 U.S.C. §§ 352(a), 352(n)) require Defendant to fully and accurately disclose information in Defendant's possession relating to the efficacy of Avandia, as well as information relating to adverse events associated with Avandia use, including but not limited to cardiovascular events. These disclosures must appear in the Avandia Package Insert ("Avandia PI"), other labeling, and promotional materials.

44. Sections 502(a) and 201(n) of the FDCA (21 U.S.C. §§ 352(a) and 321(n)) prohibit Defendant from claiming efficacy or minimizing risks of adverse events, and from making misleading claims that Avandia is safer or more effective than other available medications.

45. Defendant violated Sections 502(a) and 201(n) of the FDCA (21 U.S.C. §§ 352(a) and 321(n)) by omitting information concerning risks and benefits from the Avandia PI and other labeling, and by utilizing and/or distributing promotional materials

that were false and misleading regarding Avandia's efficacy and effectiveness.

46. Furthermore, Defendant minimized the risks of these serious adverse events, failed to advise consumers and physicians to monitor patients for these adverse events, and otherwise falsely claimed that Avandia was safer and more efficacious than other medications available on the market. Thus, the information disseminated by Defendant was not fair and balanced.

**B. Avandia's Factual Background**

**1. Diabetes and Cardiovascular Risk**

47. Type II diabetes is a serious and life threatening disease that affects approximately 18 to 20 million Americans. Type II diabetes is a medical condition where the patient becomes resistant to his/her endogenous insulin. Insulin is necessary to enable the transport of sugar (generated from food and drink) from the blood into the cells. Without insulin, sugar builds up in the bloodstream and the cells are starved for energy. This can cause tissue breakdown which in turn can lead to kidney failure, blindness, amputations, heart attacks and stroke. When a patient's insulin resistance results in a fasting blood glucose in excess of 126 mg/dl for two consecutive days, the subject patient is classified as having Type II diabetes.

48. Cardiovascular disease is the leading cause of death for persons with Type II diabetes and more than 65 percent of persons with diabetes will die from a heart attack or stroke. *See* http://www.diabetes.org/type-2-diabetes/well-being/heart-disease-and-stroke.jsp. Thus, the primary goal of any diabetes treatment should be the reduction of this cardiovascular risk. *See* Scott M. Grundy, et al. "Diabetes and Cardiovascular Disease, A Statement for Healthcare Professionals From the American Heart

Association." *Circulation* 1999; 100: 1134-1146.

49. Type II diabetic patients have a wide array of pharmaceutical treatment options available to them including, but not limited to, insulin, alpha-glucosidase inhibitors, biguanieds, meglitinides, sulfonylureas and thiazolidinediones.

**2. TZDs and Treatment of Type II Diabetes**

50. TZDs, also referred to as "Insulin Sensitizers," are a class of drug which includes Avandia, Actos® (pioglitazone) and Actosplus met (pioglitazone and metformin). First manufactured in the 1990s, and considered a new treatment for Type II diabetes, TZDs are a novel class of insulin-sensitizing agents which work in part by increasing cell sensitivity to insulin. TZDs lower blood sugar levels, and enable the body to more effectively use insulin by reducing insulin resistance in the body.

51. As a TZD approved on May 25, 1999, Avandia is prescribed for the management of Type II diabetes mellitus or NIDDM.

52. Avandamet was approved by the FDA on October 10, 2002 as a combination of Avandia and metformin in one single pill; Avandament is indicated to treat Type II diabetes.

53. Avandaryl was approved by the FDA on November 23, 2005 as a combination of Avandia and glimepiride in one single pill; Avandaryl is indicated to treat Type II diabetes.

54. Despite the fact that Avandia lowers blood glucose levels in Type II diabetes patients, at least 42 studies have shown that use of Avandia dramatically increases the risk of cardiovascular events in Type II diabetes patients.

55. One potential contributing factor may be the adverse effect of Avandia on

serum lipids. Studies of Avandia users illustrate an increase in LDL cholesterol, as compared with a placebo. In fact, Avandia's product labeling states that Avandia increases LDL cholesterol.

56. Elevated levels of LDL cholesterol are associated with an increase in adverse cardiovascular outcomes. Thus, an increase in LDL cholesterol of the magnitude observed in Avandia may have contributed to adverse cardiovascular outcomes.

57. One researcher has indicated:

> [R]osiglitazone [Avandia] was approved on the basis of its ability to improve glycemic control, a surrogate endpoint. Because high glucose levels increase the risk of vascular disease, a glucose-lowering drug is presumed to reduce the risk of major adverse health outcomes such as myocardial infarction [heart attack]. **Rosiglitazone however, appears to be associated with an increase rather than a decrease in the risk of myocardial infarction [heart attack].**[3]

58. Nevertheless, Defendant downplayed the significance of the increase in LDL by characterizing the LDL attributed to Avandia as "fluffy" or non-atherogenic LDL, which would not increase the risk of cardiovascular events.

59. Defendant also assured physicians that these studies only illustrate a very slight increase in LDL levels, and continued to promote Avandia as a superior and effective drug for diabetic patients.

60. Moreover, studies illustrate Avandia increases apoB levels as well as LDL particle numbers. *See* Linda von Wartburg. "Updated: Analysis Associates Avandia With Greater Risk of Heart Attack," Diabetes Health May 31, 2007. *See* http://www.diabeteshealth.com/read/2007/05/31/5204/updated-analysis-associates-

[3] *See* Psaty Bruce M., et al., Editorial: "The Record on Rosiglitazone and the Risk of Myocardial Infarction." *New England Journal of Medicine* 357: 67-69 (5 July 2007) number 1 (emphasis added)

avandia-with-greater-risk-of-heart-attack/.

61. ApoB is the structural protein for the low-, intermediate- and very low-density lipoproteins (LDL, IDL and VLDL, respectively) ("bad" cholesterol). In general, apoB-containing lipoproteins carry lipid from the liver (apoB-100) and gut (apoB-48) to the sites of utilization. Apo AI is the active ingredient in HDL (high-density lipoprotein), helping to transport excess cholesterol from cell surfaces to lipoprotein particles for its transfer to the liver and has anti-inflammatory and anti-oxidant properties which contributes to its cardioprotective role.

62. Additionally, the activity and mass of lipoprotein-associated phospholipase A2, an inflammatory enzyme expressed in atherosclerotic plaques, shows continuous associations with risk of coronary heart disease.[4]

63. Monitoring apoB levels, along with other lipids tests such as LDL cholesterol, helps to determine an individual's risk of developing cardiovascular disease.

64. Several large-scale population studies confirmed that measurements of apo AI and B could be taken with a high degree of accuracy and precision[5] and are more accurate that those of direct HDL- C and direct LDL-C.

65. Furthermore, at least one "study indicates that apoB may be a better predicator of cardiovascular disease risk" than "bad" cholesterol. Steve Haffner, M.D.

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Avandia users can develop CAD.

[4] D. Sennik. "Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies." *Lancet* 375: 2010: 1536 – 44 .

[5] P.S. Bachorik, K.L. Lovejoy, M.D. Carroll, C.L. Johnson. "Apolipoprotein B and AI distributions in the United States, 1988–1991: results of the National Health and Nutrition Examination Survey III (NHANES III)." *Clin Chem*: 43: 1997: 2364–78; I. Jungner, S.M. Marcovina, G. Walldius, I. Holme, W. Kolar, E. Steiner. "Apolipoprotein B and A-I values in 147,576 Swedish males and females, standardized according to the World Health Organization-International Federation of Clinical Chemistry First International Reference Materials." *Clin Chem*: 44: 1998: 1641–9; J.H. Contois, J.R. McNamara, C.J. Lammi-Keefe, P.W.F. Wilson, T. Massov T, E.J. Schaeffer. "Reference intervals for plasma apolipoprotein A-I determined with a standardized commercial immunoturbidimetric assay: results from the Framingham Offspring Study." *Clin Chem*: 42: 1996: 507–14.

"ApoB: better marker for heart disease than "bad" cholesterol," *See* http://www.americanheart.org/presenter.jhtml?identifier=3022935.

66. Although diabetes causes an increase in apoB, further increases in apoB levels and decreases in apo AI levels contributes to long-term cardiovascular complications in diabetics.

67. Despite these facts, Defendant failed to mention Avandia's propensity to increase apoB levels and the associated cardiovascular risks on its labels.

68. One Cleveland Clinic physician described the absurdity of GSK's position regarding the benefits of Avandia as follows:

> The majority of patients who have diabetes eventually die of cardiovascular events. If the ultimate goal is to reduce deaths from cardiovascular events, prescribing a drug that increases the incidence of stroke and myocardial infarction in a significant number of patients doesn't make sense. **A patient doesn't care about blood sugar if he or she is having a heart attack.**

Michael A. Lincoff. "Diabetes Drugs in the Spotlight." *Cleveland Clinic Cardiac Consult* Winter 3 (2007) (emphasis added).

### C. Defendant's Knowledge of Avandia's Safety Risks and Defendant's Deliberate Decision to Disseminate False and Misleading Scientific, Medical and Clinical Data Regarding Avandia's Efficacy and Effectiveness

69. Defendant knows, and has known, that the FDA prohibits drug manufacturers from promoting and marketing drugs for uses not proven to be efficacious, effective and/or safe.

70. Defendant knows, and has known, that Avandia is not efficacious, ineffective and associated with numerous safety risks. Nevertheless, the fraudulent scheme devised by Defendant not only misrepresented not only the scientific data

regarding Avandia, but also the true creator and promoter of that information.

### 1. Pre-Approval Signals of Avandia's Risks

71. Prior to approval, Avandia underwent a FDA Medical Officer Review (MOR). Avandia's MOR was completed on April 16, 1999. Even at this early stage, GSK was alerted to the cardiovascular risks associated with its drug. The reviewing officer stated as follows: "The major issues regarding safety of rosiglitazone relate to hepatitis, edema, anemia and the heart." *See* Robert Misbin, MD. "Medical Officer's Review of New Drug Application." April 16, 1999 at 26.

72. Regarding one study, the MOR stated: "Safety: The only safety issue noted in this study is that 6 patients on 4 mg bid had cardiac events including two myocardial infarctions." *Id.* Additionally, under the Safety/Cardiac Abnormalities section of the review, the reviewer stated as follows:

> Acute myocardial infarctions occurred in 22 patients (0.5%) of patients on [Avandia] and was fatal in six. This result would appear somewhat higher than in other treatment arms . . . .

*Id.* at 28.

73. Given these early signals of cardiovascular risk, the reviewing officer stated that, as a condition for approval, the company needed to conduct a post-marketing study to better assess this risk. *Id.* at 41.

74. Rather than complying with the reviewing officer's mandate, GSK refused to undertake the study because it was too expensive. As support for its decision to forego performing the study, Defendant stated, "given the scope, complexity, and expense of such trials, [GSK] is not currently in a position to make any commitment about a long term outcomes trial." Letter to Jena Weber from Clare Kahn, re: NDA 21-071 – Request for Revised Annotated Labeling and Outline of Phase IV Commitments

dated May 5, 1999.

75. With this, the first chance to protect consumers was, at best, ignored.

**2. Early Post-Approval Signals of Avandia's Risks**

76. Since approval in 1999, the FDA has been monitoring controlled clinical trials and post-marketing reports related to Avandia which have revealed several heart-related adverse events (e.g. fluid retention, edema, and congestive heart failure ("CHF")).

77. For example, almost immediately after its 1999 approval, Avandia's cardiac safety profile was questioned. In the year of its release, John Buse, M.D., Ph.D, a world-famous endocrinologist and a former president of the American Diabetes Association, opined that Avandia may carry cardiovascular risks. At the time Dr. Buse discovered his findings and reported them to GSK, he was an investigator for a GSK study on Avandia.

78. GSK reacted to these criticisms by threatening Dr. Buse with a lawsuit. *See* Dr. Buse's testimony before the Committee on Oversight and Government Reform on June 6, 2007.

79. In response to GSK's pressure, Dr. Buse sent a three-page letter to Dr. Tadataka Yamada, GSK's Chairman of Research and Development. In the letter, Dr. Buse wrote, "I may disagree with GSK's interpretation of that data [but] I am not for sale.... Please call off the dogs. I cannot remain civilized much longer under this kind of heat." Letter (approximately June 28, 1999) from Dr. Buse to Dr. Yamada regarding his presentation at the Endocrine Society and American Diabetes Association.

80. On March 15, 2000, Dr. Buse wrote a letter to the FDA stating that he

was concerned GSK had "overstated the safety of [Avandia] with respect to cardiovascular issues" because studies reflected a "worrisome trend in cardiovascular deaths and severe adverse events" associated with the drug. Dr. Buse letter to Dr. Jane Henney, FDA re: Citizen's Petition to Immediately Require Class Labeling for the Diabetes Drugs Troglitazone (Rezulin), Rosiglitazone (Avandia) and Pioglitazone (Actos)" dated March 15, 2000.

81. GSK's attempt to silence Dr. Buse was the subject of a congressional inquiry. In November of 2007, the U.S. Senate Committee on Finance issued a Staff Report which called GSK's response to Dr. Buse's concerns an "extremely serious" and revealed an "orchestrated plan to stifle the opinion" of a professor of medicine who specializes in diabetes. Committee Staff Report to the Chairman and Ranking Member, Committee on Finance, United States Senate, "The Intimidation of Dr. John Buse and the Diabetes Drug Avandia" dated November 2007.

82. The Committee Staff Report noted that GSK's campaign to silence Dr. Buse involved "executives at the highest levels of GSK," including then and current Chief Executive Officer Jean-Pierre Garnier. *Id.* The Committee remained concerned that GSK had not altered its corporate culture in the years since the attacks on Dr. Buse (1999-2000) because "GSK's behavior since the Committee first brought these allegations to light has been less than stellar. Instead of acknowledging the misdeed to investors, apologizing to patients, and pledging to change corporate behavior, GSK launched a public relations campaign of denial." *Id.*

83. Additionally, a November 19, 2008 *Wall Street Journal* article states that, Dr. Mary Money of Hagerstown, Maryland, observed problems with Avandia shortly

after it entered the market in 1999 and attempted to warn GSK in 2000. According to the article, Dr. Money linked Avandia to congestive heart failure when a patient had begun taking Avandia two weeks earlier, and an echocardiogram showed high pressure in the arteries of the lungs.

84. GSK rejected Dr. Money's warning and tried to make her stop talking about it with other doctors and hospitals, according to documents and interviews. GSK defends its effort, which it says was an attempt to correct "inaccuracies."

85. In February 2002, GSK submitted a supplemental New Drug Application (sNDA) seeking approval for the use of Avandia in combination with insulin. In response to this application, the FDA asked the company to submit additional information on adverse events from follow-up trials it had performed. The results showed that "approximately 10% of patients treated with rosiglitazone and insulin experienced **cardiac AEs** [adverse events] across the trials to date." Memorandum from the FDA re: NDA review issues and recommended action, dated February 26, 2003 (emphasis added).

86. Additionally, the FDA memorandum noted that, given the earlier signals, an increase in cardiovascular risk was not unexpected. It stated:

> [W]hile the signal of increased risk for edema, CHF [congestive heart failure], and other CV [cardiovascular] adverse events persists in these follow up trials (indeed, there was no expectation that it was a fluke of the earlier trials and would disappear in subsequent studies), a strategy of careful patient selection (e.g., no history of cardiac compromise), judicious titration, and monitoring may obviate some of the fluid-related AEs of the combination.

After reviewing GSK's application, the FDA's Medical Team Leader stated "there was a marked increase in total adverse cardiac events, serious adverse cardiac events, and

adverse cardiac events leading to withdrawal in patients on insulin and Avandia combination therapy compared to insulin alone (14% vs. <5% respectively)." Memorandum from the Medical Team Leader to the Division Director at the FDA re: Team Leader Recommendation, dated February 7, 2001.

87. Based on this information, the FDA's Medical Team Leader recommended **against** approving GSK's application for combination therapy with insulin, stating that "although the sponsor has shown that Avandia is effective in providing better glucose control when added to insulin, the safety information that emerged from the studies is quite troublesome." *Id.* In addition to recommending against approval, the Medical Team Leader also recommended that the company consider sending a letter to medical doctors warning them of the dangers associated with combining Avandia and insulin therapies.

88. The data also showed that Avandia study subjects and users experienced improvement of symptoms upon cessation of Avandia consumption. The same memorandum also stated that "[t]his case series suggest [CHF] may be occurring in individuals without previously diagnosed disease."

89. Despite these concerns and over the Medical Team Leader's objections, GSK secured the approval for use with insulin. GSK had ignored another signal.

90. The FDA then requested that Defendant make a change to Avandia's prescribing label to warn doctors that the drug could cause fluid retention. In most cases, CHF is a process that occurs over time, when an underlying condition damages the heart or makes it work excessively hard, weakening the organ. CHF is characterized by, among other symptoms, abnormal fluid retention, which usually results in swelling

(edema) in the feet and legs.

91. However, shortly after this regulatory request, GSK's sales representatives denied the existence of serious risks associated with Avandia during oral presentations at a medical convention. The FDA sent a "Warning Letter" to GSK instructing Avandia to, among other things, order its sales representatives and marketers to stop denying or minimizing the risks of heart attacks and heart-related diseases in patients.

92. Defendant's concealment was also discussed in a June 1, 2007 article published by *Bloomberg News* which stated that, in 2005, Defendant performed a review and found that Avandia raised the risk of heart attacks by 31%. Defendant gave the review to the FDA and, while including the information on its website, Defendant buried the information amid information concerning more than 2,000 studies.

93. According to that same article, Defendant stated that the heart-risk studies, including Defendant's own, are flawed and GSK did not believe it was obligated, or legally required, to highlight every study done on its drugs. As Jean-Pierre Garnier, the Chief Exeutive Officer of GlaxoSmithKline PLC, told reporters at the company's annual meeting on May 23, 2007 in London, "Why would you publicize it [?]. . . We don't publicize every submission we make to the Food and Drug Administration."

### 3. Pre-2007 FDA Hearing Studies Confirming Defendant's Knowledge of Avandia's Risks

94. More early signals known to GSK concerning Avandia's cardiovascular risks were also revealed, confirmed and made public.

95. A 12-week study from March 2006 (and only uncovered recently)

entitled, "A 12-Week Randomized, Double-Blind, Local Multicenter, Placebo-Controlled Study To Evaluate The Efficacy, Safety And Tolerability Of Rosiglitazone (BRL 49653C) When Administered Once Daily To Patients With Type-2 Diabetes Mellitus (T2DM) Who Are Inadequately Controlled On At Least Half Maximal Dose of Usual Sulphonylurea," revealed adverse events in 98% of those patients taking Avandia. This study was conducted to evaluate the safety and efficacy of Avandia in combination with sulphonylurea in subjects with Type II diabetes, and to determine if the combination has an additive effect. The study reported an approximate 24% increase in LDL and 10% decrease in HDL levels after 12 weeks.

96. In April 2006, the FDA required labeling for Avandia to be updated to include new data in the WARNINGS section about a potential increase in heart attack and heart-related chest pain in some patients. This change was based on the results of a controlled clinical trial in patients with existing CHF. A higher number of heart attacks or angina was observed in patients treated with Avandia compared to those treated with a placebo. Angina is chest pain or discomfort that occurs when an area of the heart muscle does not receive enough oxygen-rich blood. In most cases, the lack of blood supply is due to a narrowing of the coronary arteries as a result of arterosclerosis.

97. Within the next year, Steven E. Nissen, M.D., and Kathy Wolski, M.P.H., tabulated and compiled a meta-analysis[6] using published literature, the FDA website and a clinical-trials registry maintained by Defendant. Drs. Nissen and Wolski used 116 potentially relevant studies, and 42 trials comprising approximately 28,000 people who

[6] Meta-analysis is the systematic method of evaluating statistical data based on the results of several independent studies of the same problem. *See* http://medical-dictionary.thefreedictionary.com/meta-analysis.

took Avandia and that met the inclusion criteria, including a study with a duration of more than 24 weeks, which used a randomized control group not receiving Avandia.

98. The study, entitled *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes* (the "Nissen Study"), was published on May 21, 2007 in the *New England Journal of Medicine*. It revealed that Avandia was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from heart attacks and heart-related diseases. Specifically, the meta-analysis revealed a **43% higher risk of heart attack** for those taking Avandia compared to people taking other diabetes drugs or no diabetes medication: people taking Avandia suffered such adverse events at a rate of 1.99%, as opposed to 1.51% for other patients.

99. Instead of a responsible and reasoned response to this study, GSK took steps to encourage aggressive prescribing and dispensation of Avandia for persons to whom it posed grave health dangers. *See infra.*

100. Based in part on the Nissen Study, on May 21, 2007 the FDA issued a new safety alert that addressed potential safety issues stemming from the pooled analysis of previously completely controlled clinical trials demonstrating a potentially significant increase in the risk of heart attack and heart-related diseases in patients treated with Avandia.

101. On May 23, 2007, consistent with recommendations made by senior FDA staff at an internal regulatory briefing held the prior month, the FDA issued letters to Defendant requesting that Avandia's product labeling include a black box warning to more prominently address the risks of heart failure associated with the use of Avandia.

Although this risk was already contained in the WARNINGS section of the Avandia PI, the FDA decided to make this request because, despite the existing warnings, these drugs were being prescribed to patients with significant heart failure.

102. Right on the heels of these studies and FDA pronouncements, Defendant engaged in a massive publication and advertising campaign designed to bolster consumer confidence in Avandia.

103. For example, on and around June 5, 2007, GSK published full-page advertisements in more than a dozen major U.S. newspapers touting Avandia in an attempt to reassure patients of the safety of Avandia.

104. This advertising and promotional campaign consisted of advertisements, promotional literature for doctors and other health care providers, and other direct to consumer promotional materials to be provided by Defendant to potential users of Avandia.

**4. Congressional, Regulatory and Industry Reaction**

105. On June 6, 2007, sparked by the publication of the Nissen Study, the House Committee on Oversight and Government Relations held a hearing to examine how the FDA had assessed the safety of Avandia.

106. During the hearing, the FDA announced that a meeting would be held on July 30, 2007 to discuss the risk of heart attacks and heart-related disease associated with thiazolidinediones, with a focus on Avandia.

107. Further, U.S. Senator Chuck Grassley revealed, in a statement published in late July 2007, that a senior FDA scientist had recommended a black box warning for Avandia in February 2006. However, the FDA allegedly removed that scientist,

Rosemary Johann-Liang, from work on Avandia after she voiced concerns about the safety of the drug.

108. According to Senator Grassley's statement, the FDA did not act on the recommendations from Dr. Johann-Liang. The statement did not say why the FDA took no action on the advice.

109. On July 30, 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA convened in Gaithersburg, Maryland (the "July 30th Hearing") to discuss the myocardial ischemic risk associated with rosiglitazone treatment in patients with Type II diabetes mellitus. Both the FDA and GSK made presentations at this hearing.

110. The joint committee consisted of 24 experts in cardiovascular disease, epidemiology, biostatistics, and endocrinology. Approximately ten indivduals presented testimony during the all-day hearing.

**a. FDA's Dr. David Graham Calls for Avandia Removal**

111. David J. Graham, M.D., M.P.H. of the FDA Office of Surveillance and Epidemiology presented the following results of the FDA's meta-analysis of Avandia data at the July 30th Hearing:

- FDA meta-analysis shows a 20% to 68% increased cardiovascular risk with six to twelve months of Avandia use compared to non-use;
- Avandia increased risk of ischemic heart disease by 40% compared with comparator drugs and by 70% compared with placebo;
- Compared to pioglitazone (Actos), Avandia increases the risk of a cardiovascular event over three and half times;

- The data indicates that since its introduction to the market Avandia use caused between 66,000 and 205,000 cardiovascular events that otherwise would not have occurred.

112. At the July 30th Hearing, Dr. Graham concluded that Avandia should be pulled from the market.

113. Referring to a host of cardiovascular adverse events including heart attacks, Dr. Graham stated "[t]here is no evidence, none whatsoever, to support the benefits of rosiglitazone with these outcomes." Best case scenario for GSK, Dr. Graham said, was that Avandia was responsible for 40,000 excessive cardiovascular events in 6.5 years since 1999. Dr. Graham put the real number at 80,000 excess cases. Transcript from the FDA Advisory Committee Hearing, dated July 30, 2007 at 229, 231.

**b. Public Citizen Calls for Avandia Removal**

114. Sidney Wolfe, M.D., Elizabeth Barbehenn Ph.D. and Ben Wolpaw, members of Public Citizen's Health Research Group ("Public Citizen"), also presented testimony at the July 30th Hearing.

115. Public Citizen revealed many of the early signals of Avandia's significant cardiac adverse effects including a 1999 FDA pharmacology review of animal toxicity in rosiglitazone use and anticipated potential human toxicities. As a result, the FDA pharmacologist recommended not to approve rosiglitazone for the proposed indication for long-term human use.

116. Additionally, Public Citizen stated that due to the ubiquitous nature of Peroxisome proliferator-activated receptor (PPAR gamma), the receptor which Avandia acts upon and is expressed in many tissues, it was hardly surprising Avandia was

causing patients so many significant kinds of damage (e.g., cardiac, liver, bone, bone marrow).

117. Public Citizen demonstrated that when Avandia binds to the PPAR gamma receptors, those receptors react and bind to DNA, initiating gene expression. The effect is to lower plasma glucose, but it also causes the cardiac cells to produce and store fat. This results in the cells becoming fatty and dying off. Myocardial contraction is disrupted, and the development of heart failure appears to occur.

118. The members of Public Citizen also stated that the increased risk of ischemic heart disease, including myocardial infarctions, justifies the removal of the drug from the market.

**c. GSK's DREAM and ADOPT Studies**

119. During the hearing, in response to those opposing Avandia continuation on the market, GSK presented the results of two industry-sponsored studies, DREAM and ADOPT, claiming these studies did not suggest a large cardiovascular risk. However, as the FDA pointed out, neither study adequately addressed the cardiovascular risk issue.

120. The DREAM study endeavored to determine whether use of Avandia *before a patient was diagnosed with diabetes* would prevent the onset of the disease. H.C. Gerstein, et al. "DREAM (Diabetes Reduction Assessment with Ramipril and rosiglitazone Medication) Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial." *Lancet* 368: 2006:1096-105. Hence, the study population *did not have diabetes.*

121. The Advisory Committee recognized this weakness in GSK's

presentation:

> [T]he committee expressed concern that these trials [DREAM and ADOPT] do not study the patients of interest, and in fact, excluded the patients that we are concerned about [*i.e., persons with diabetes*]; **therefore lack of a signal for the outcomes in these trials may not necessarily inform decisions regarding risk for Avandia.**

Summary Minutes of the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, July 30, 2007 (emphasis added).

122. Dr. Nissen later noted that, even with this relatively healthier *pre-diabetes* patient population, DREAM reflected increased cardiovascular risks. He wrote as follows:

> In DREAM, despite a substantial delay in onset of diabetes, rosiglitazone resulted in a **37% increase in adverse cardiovascular events**, a finding that very nearly reached conventional levels of significance. This trend virtually precludes the possibility of an overall benefit and suggests an unexpected mechanism for harm.

Nissen SE. "The DREAM trial." *Lancet* 368: 2006: 2049 (emphasis added).

123. In fact, Dr. Nissen questioned the entire basis of the DREAM study in that it was designed, not to treat diabetes, but to treat "pre-diabetes" -- a non-existent illness.

> In the absence of evidence of actual health benefits, the public health rationale for the use of a drug to treat a precondition and thereby to prevent the onset of a related condition that would, normally and simply, mark the beginning of drug treatment is not clear. **The DREAM study represents an effort to medicalize a predisease state.**

*Id.* (emphasis added).

124. The ADOPT study, also relied upon by GSK at the July 30th Hearing also failed to support its position. Again, the Committee noted that the study did not

provide valuable information to test the cardiovascular safety of Avandia as it was not designed to record cardiovascular outcomes. As one researcher noted:

> The manufacturer did not make a serious effort to verify the presumed health benefits of rosiglitazone in a timely fashion. In ADOPT.... [cardiovascular] events were not identified or recorded in a systemic fashion, and heart failure was the only outcome that was reviewed and adjudicated at the end of the trial. Nonetheless... rosiglitazone in ADOPT was associated with a higher risk of cardiovascular events [than the comparator drug].

Psaty B, Editorial: "The Record on Rosiglitazone and the Risk of Myocardial Infarction." *New England Journal of Medicine*, 357:15 July 2007: 67-69.

125. At the July 30th Hearing, the advisory committee made the non-binding recommendation, based on a 22 to 1 vote, that Avandia should remain on the market. However, the committee also voted 20 to 3 in agreement that available data shows that the cardiovascular risk associated with Avandia is greater than with other available therapies for the treatment of Type II diabetes.

126. The advisory committee also overwhelmingly urged that the FDA require GSK to apply a "black box warning" for Avandia – the strictest warning the FDA can issue.

127. Clifford J. Rosen, M.D., chairman of the committee and an osteoporosis and endocrinology expert at the Maine Center for Osteoporosis, stated that "there was enough concern on the advisory committee that virtually everybody felt there was risk." Dr. Rosen predicted that "there's going to be changes in the way [Avandia] is promoted ... and certainly in how physicians use this drug."

128. On August 14, 2007, the FDA issued a press release indicating that GSK had agreed to strengthen Avandia's label to add a "black box label" concerning the risk of heart failure. The FDA stated that "The upgraded warning emphasizes that [Avandia]

may cause or worsen heart failure in certain patients."

129. Further, the FDA advisory panel is scheduled to hold another hearing in July 2010 to consider the results of new Avandia studies.

### 5. Post-FDA Hearing Studies and Petitions for Avandia Removal

130. The September 12, 2007 issue of the Journal of American Medical Association ("JAMA") published a study that found that Avandia doubled the risks of heart failure and raised the risks of heart attack by 42% (the "JAMA Study"). S. Singh, et al. "Long Term Risk of Cardiovascular Events with Rosiglitazone." *Journal of the American Medical Association* 298: 2007: 189-1195.

131. The JAMA Study, which consisted of a *third* meta-analysis, confirmed both the Nissen analysis and the FDA's results showing a **42% increase** in myocardial infarction associated with Avandia use. The study concluded "rosiglitazone significantly increased the risk of myocardial infarction."

132. Sonal Singh, M.D., a professor and board-certified Internal Medicine at the Wake Forest School of Medicine, was the co-author of the JAMA Study. Dr. Singh stated: "If you use Avandia to treat patients with Type 2 diabetes their chance of getting heart failure due to Avandia is one in 30 and their risk of getting a heart attack is one in 220. All due to the drug."

133. Subsequent studies have supported these three meta-analyses. For example, a Canadian study described as "independent" and "not funded by industry, and ... huge" examined "real-life data" for nearly 160,000 patients and reached similar conclusions reflecting a **40% increase** of heart attack risk in Avandia users.

Lipscombe, et al. "Thiazolidinediones and Cardiovascular Outcomes in Older Patients with Diabetes." *Journal of the American Medical Association* 298: 2007: 2634-2643.

134. The lead author stated as follows:

> Our larger, well-designed population-based study provides more convincing evidence that [Avandia] is associated with in increased risk of cardiac events and deaths among elderly patients with diabetes. Moreover, the magnitude of association between TZDs and adverse outcomes, was consistent with risks reported elsewhere.
>
> Current treatment with TZD monotherapy was associated with a significantly increased risk of congestive heart failure . . . acute myocardial infarction . . . and death . . . compared with other oral hypoglycemic agent combination therapies. . . The increased risk of congestive heart failure, acute myocardial infarction, and mortality associated with TZD use appeared limited to rosiglitazone [Avandia]. *Id.*

135. On September 29, 2007, a study published in the medical journal *Lancet* found that patients with a history of heart disease and heart failure have as high as a **72%** increased risk of heart failure while taking Avandia.

136. The study was conducted by pooling data from seven different clinical trials to study the risks of Avandia and Actos, another diabetes drug. Researchers from the Lahey Clinic in Massachusetts included more than 20,000 patients who, during the study, were given either Actos or Avandia to treat Type II diabetes.

137. In addition to its deleterious effects on the heart, Avandia can cause blindness and doubles the risks of bone fractures in women.

138. On October 17, 2007, the U.S. Department of Veterans Affairs ("VA") announced that after its own review, it concluded that, for some patients, rosiglitazone may not afford the same margin of safety as alternative drug therapies.

139. The VA stated that Avandia would be available for patients already using it, if they decided to continue; however, the VA urged doctors to inform patients about

Avandia's risks and benefits. The VA also stated that it "will not provide it [Avandia] to patients for whom it is not currently prescribed." Thus, the VA effectively dropped Avandia from its formulary for new patients.

140. Shortly after, the VA's decision to limit Avandia, two U.S. pharmacy benefit managers, Prime Therapeutics and HealthTrans, dropping Avandia from their national formularies after a thorough analysis of the clinical literature examining Avandia's safety and efficacy. This was reported by Reuters in a December 6, 2007 article.

141. Other health insurers like Kaiser Permanente and governments including the County of Santa Clara have also removed Avandia from their formularies.

142. Remarkably, despite the overwhelming evidence, GSK continued to deny that there was evidence of an increased heart risk with Avandia. For example, in December 2007, instead of admitting that Avandia posed a risk to its users and warning the public of its dangers, GSK published the following statement:

> Across multiple sources of data, there is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial ischemic events or deaths in comparison to other anti-diabetic agents.

Press Release: "GlaxoSmithKline responds to JAMA article on the ICES thiazolidinediones and cardiovascular outcomes in older patients with diabetes," dated December 11, 2007.

143. In October 2008, Public Citizen petitioned the FDA to immediately ban Avandia based on the clear evidence of increased risk of heart attacks, heart failure, bone fractures, anemia and macular (retinal) edema with vision loss. The petition also stated that the evidence for Avandia's toxicities is compounded by the accompanying

lack of evidence of any clinical benefit, compared to other approved drugs for diabetes, such as metformin, insulin and sulfonylureas.

144. Moreover, a June 5, 2009 *Forbes* article describes GSK's failed attempt to dismiss charges that Avandia raises the risk of heart attacks. Unveiling results of a large 4,447-patient study called RECORD, GSK attempted to combat the Nissen Study by showing that there is no difference in the rates at which patients were hospitalized for or killed by heart disease whether they were on a drug combination that contained Avandia or not. However, the RECORD study ignored a key fact: 40% of patients analyzed in the study were not taking Avandia at the study's end. GSK's study also had another problem – patients on Avandia took 10% more cholesterol-lowering drugs, which reduces the rate of heart attack and makes the trial worthless or questionable at best.

145. Also, some doctors examined the results and believed that the study actually showed slightly more heart problems with Avandia - a bad sign even if the difference was so small that it could have occurred by chance alone. "This study, which was designed to show the benefit of rosiglitazone (Avandia), if anything shows the opposite," said Dr. David Nathan, M.D., chief of diabetes care at Massachusetts General Hospital. Dr. Nathan has no role in the study nor financial ties to any diabetes drug maker.

146. Furthermore, a May 6, 2009 study also showed Avandia increases apoB levels, increases LDL particle numbers, and the increased apoB levels' association with cardiovascular risks in Type II diabetes. *See* Seth S. Martin, *et al.*, "Apolipoprotein B but not LDL Cholesterol is Associated with Coronary Artery Calcification in Type 2

Diabetic Whites." *The American Diabetes Association* 58: 2009: 1887-1892. *See* http://diabetes.diabetesjournals.org/content/58/8/1887.abstract. Defendant failed to warn patients and doctors of the increased apoB levels contributing to cardiovascular events.

147. Despite knowledge of the widespread health dangers of Avandia, Defendant failed to effectively warn consumers about the use of this drug as compared to other competing formulations which posed much lesser health risks.

### 6. January 2010 Senate Staff Report Reveals Defendant Knew about Avandia's Cardiovascular Risks for Years But Failed to Warn Patients and the FDA

148. Triggered by the May 2007 study published in the *New England Journal of Medicine*, in January 2010, the U.S. Senate Staff Committee on Finance published the "Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia." ("Senate Report on Avandia"). The staff report was developed by the U.S. Senate Committee on Finance who reviewed documents provided by Defendant, the FDA, and others and conducted numerous interviews and phone calls with Defendant, the FDA, and an anonymous whistleblower.

149. The staff report reveals,

> . . . the reviewed evidence suggests that **GSK knew for several years prior to this study that there were possible cardiac risks associated with Avandia**. As a result, **it can be argued that GSK had a duty to warn patients and the FDA of the Company's concerns**. Instead, **GSK executives attempted to intimidate independent physicians, focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk**, and **sought ways to downplay findings that a competing drug might reduce cardiovascular risk.**

Sen. Max Baucus and Sen. Chuck Grassley, Staff Rep. On GlaxoSmithKline and the

Diabetes Drug Avandia, S. PRT. 111-41, 111th Cong. 2d Sess., at 1 (2010) (emphasis added).

150. The Senate Report on Avandia revealed that in December 2007, Dr. Steve Haffner, a professor of medicine at the University of Texas Health Sciences Center, San Antonio, and a consultant for Defendant, leaked to Defendant the draft *New England Journal of Medicine* Nissen study critical of Avandia. Dr. Haffner was entrusted with a confidential copy of the manuscript draft because he was peer-reviewing the study. The leaked manuscript was widely disseminated within the company, and allowed Defendant to launch a public relations plan to protect Avandia, a multi-billion dollar product.

151. Furthermore, the Senate Report on Avandia revealed Defendant was aware since at least 2004 that the RECORD trial was statistically inadequate, or "underpowered" to answer questions regarding cardiovascular safety and the report states that "inconclusive" results could be favorable to GSK and the marketing strategy for Avandia.

152. According to the Senate Report on Avandia, experts were advising Defendant since 2004 about the possible biological mechanisms related to why Avandia may cause an increased risk for heart attacks. However, Defendant appeared eager to design studies to prove that Avandia was safer than its competitor Actos.

153. Furthermore, in late 2005, Defendant published a draft retrospective analysis of cardiovascular events in Avandia clinical trials discussing the underlying cause for the increase in ischemia. In the analysis that examined myocardial ischemia, the authors mention a "hypothesis that small degrees of fluid retention may be an

important contributor to the development of worsening myocardial ischemia in high risk patients."

154. According to the Senate Report on Avandia, after Defendant reviewed the evidence found in this analysis, it appears that Defendant was aware of the potential cardiovascular risks associated with Avandia in late 2004 or early 2005.

155. Additionally, in 2005, Defendant ordered an "observational" trial study that was conducted in two parts: the first part in 2005 and the second in 2006. The results of these studies support the further investigation of the cardiovascular risks associated with Avandia.

156. According to a February 22, 2010 *New York Times* article, one internal e-mail message from the Senate Report found that Defendant's statistician stated that "there is no statistical reason for disregarding the findings" of Dr. Nissen's study. In another email, Dr. Moncef Slaoui, head of research at GlaxoSmithKline, wrote that federal drug regulators, Dr. Nissen and the company's own researchers all seemed to agree that studies of the drug showed that it substantially increased the risks of death and heart attacks, also known as ischemic events: "F.D.A., Nissen and G.S.K. all come to comparable conclusions regarding increased risk for ischemic events, ranging from 30 percent to 43 percent!"

157. On February 22, 2010, less than a month after the Senate released its scathing Senate Report, the FDA announced that it was still reviewing safety data on Avandia and that conclusions will likely be released around a public meeting scheduled for July 2010.

158. Rather than acknowledge the wrongdoing exposed in the Senate Report,

GSK instead criticized the Senate Report stating the report "mischaracterizes and distorts" the company's record. In a February 2010 press release posted on its website, Defendant condemned the highly critical Senate Report that has reignited the debate around its troubled product.

### 7. February 18, 2010 Baucus-Grassley Letter to the FDA Commissioner on the Avandia TIDE study

159. After reviewing internal GSK documents, in a February 18, 2010 letter from senior Senate members Max Baucus and Chuck Grassley to Margeret A. Hamburg, Commissioner of the FDA ("Baucus-Grassley letter"), the Senators concluded: 1) Defendant was aware of the possible cardiac risks associated with Avandia years before such evidence became public; 2) Defendant had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner; 3) Defendant's executives intimidated independent physicians and strategized ways to minimize findings that Avandia may increase cardiovascular risk; and 4) Defendant sought ways to downplay findings that Actos might reduce cardiovascular risk.

160. The Baucus-Grassley letter also revealed that in 2007, the FDA requested Defendant perform a cardiovascular safety trial, called TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation), comparing Avandia to other diabetes treatments such as Actos.

161. An October 2008 analysis by FDA safety officials raised concerns regarding the TIDE study, stating there is no evidence that Avandia confers any unique health benefits over Actos, and there is strong evidence that Avandia confers an increased risk of [heart attacks] and heart failure compared to Actos. The safety officer wrote that because of cardiovascular concerns with Avandia "the safety of the study

itself cannot be assured, and is not acceptable."

162. According to an April 19, 2010 *Wall Street Journal* article, the FDA is weighing whether to halt the TIDE safety study which involves thousands of patients taking Avandia, a decision that could also determine whether the drug stays on the U.S. market. Some scientists inside and outside the FDA have stated it is unethical to compare a drug with known cardiac risks with a seemingly safer alternative. They also say Avandia should be pulled from the market.

163. Public Citizen's primary spokesperson, Dr. Sidney Wolfe, told Congress on April 28, 2010 that the TIDE study comparing Avandia with Actos should be stopped without delay, and the group continued to advocate for Avandia's removal from the market.

164. On May 25, 2010, Dr. Ruth Macklin, a doctor at the Albert Enstein School of Medicine and member of WHO (World Health Organization) Ethical Review Committee, also wrote a letter to the FDA, labeling the TIDE trial as unethical and urging it be stopped. Dr. Macklin writes:

> One objective of the TIDE study is precisely to see how much more harm one drug [Avandia] causes than another drug [Actos]. This is not minimizing harms. It is deliberately harming subjects of research. Presumably, if the study shows that rosiglitazone causes too much harm, the FDA will determine that it should be taken off the market. But if it shows some harm, but not much more than its comparators, there will be possible benefit—but only to the pharmaceutical manufacturer.

**D. Alternatives to Avandia**

**1. Actos**

165. Physicians are free to prescribe to their patients approved drugs as they see fit to treat any condition or symptom. The medical community generally encourages

physicians to prescribe the safest, most effective and cost-efficient treatment. Research and studies have illustrated that physicians can prescribe safer and/or equally effective alternatives to treat the conditions for which Defendant has promoted Avandia.

166. Another prescription medication for Type II diabetes mellitus is Actos, a drug manufactured and promoted by Takeda Pharmaceuticals North America.

167. On March 15, 2000, Dr. Buse wrote to Dr. Jane Henney, former FDA Commissioner of Food and Drugs, and stated that "the frequency of mild and serious adverse events that I have seen with troglitazone [Rezulin®] and pioglitazone is comparable to or less than the number I have observed with other antidiabetic agents." Dr. Buse letter to Dr. Jane Henney, FDA re: Citizen's Petition to Immediately Require Class Labeling for the Diabetes Drugs Troglitazone (Rezulin), Rosiglitazone (Avandia) and Pioglitazone (Actos)" dated March 15, 2000. Rezulin was withdrawn from the U.S. market on March 21, 2000.

168. In his letter, Dr. Buse strongly suggested that Actos is one of the "most effective, safe and beneficial drugs in its class" and that Avandia "may be associated with less beneficial cardiac effects or even adverse cardiac outcomes." Dr. Buse stated he found that only Avandia had been associated with increased cardiac weight, which is another negative cardiac effect.

169. A European clinical trial called PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) has assessed the effects of Actos on mortality and morbidity associated with cardiovascular disease progression in patients with Type II diabetes.

170. The trial examined whether the observed effects of Avandia represent a

"class effect" of thiazolidinediones. The study suggested that Actos consistently improved components of diabetic dyslipidemia, another cardiovascular disease risk factor, which is characterized by low HDL ("good") cholesterol levels and high triglycerides.

171. Additionally, a June 23, 2007 *Bloomberg* article discussed a study finding Actos may lower the risk of heart attack and death by 44 percent in diabetic patients with kidney disease. The findings, from a subgroup of patients enrolled in a previous study, were reported at the June 23, 2007 meeting of the America Diabetes Association in Chicago. In a separate study, Actos reduced inflammation and blood clots more than a placebo.

172. Furthermore, a February 20, 2010 *New York Times* article discusses FDA reports with claims that if every diabetic now taking Avandia were instead given Actos, about 500 heart attacks and 300 cases of heart failure would be averted each month.

173. A June 18, 2007 *USA Today* article discusses an increased number of physcians discontinuing Avandia prescriptions and are instead prescribing Actos as an alternative diabetes medication. "Before the [*The New England Journal of Medicine*] posted the study May 21, U.S. doctors were writing about 240,000 prescriptions [of Avandia] per week, Glaxo spokeswoman Alice Hunt says. That has dropped to about 215,000 to 220,000 per week. Glaxo estimates the number of people taking Avandia has dropped from about 1 million to 900,000 in the USA." Additionally, new prescriptions for Avandia had dropped 40% as a result of Dr. Nissen's study. New prescriptions are defined as the first prescription a doctor writes for a patient even if the patient might already have been taking Avandia under a different doctor's care. "Prior to Nissen's

study, U.S. doctors wrote about 80,000 new Avandia prescriptions weekly; that number has dropped to about 55,000, Hunt says." The *USA Today* article explains that physicians are switching patients to Actos as an alternative.

174. A May 2009 Canadian study conducted by David N. Juurlink and published in *British Medical Journal* and entitled "Adverse cardiovascular events during treatment with piolitazone and rosiglitazone: population based cohort study" compared the risk of acute myocardial infarction, heart failure and death with Type II diabetes treated with Avandia and Actos in 39,736 patients aged 66 years and older between 2002 and 2008.

175. The study concluded that among older patients with diabetes, Actos is associated with a significantly lower risk of heart failure and death than Avandia and given that Avandia lacks a distinct clinical advantage over Actos, continued use of Avandia may not be justified.

176. A Johns Hopkins study published in 2009 in the *British Medical Journal* reviewed 40 randomized, controlled trials involving cardiac risks of older and newer diabetes drugs and found that metformin hydrochloride was the only drug associated with a decreased risk of cardiovascular mortality compared with any other oral diabetes agent or placebo. "The only diabetes drug with increased cardiovascular risk was rosiglitazone (Avandia), for which the increased risk was 1.68, falling just short of statistical significance," Dr. Wolfe said. "Pioglitazone (Actos) had neither increased nor decreased cardiovascular risk in the six randomized trials that comprised the study.

177. Thus, Actos has fewer cardiac risks than Avandia and may prove to be a safer alternative to Avandia for the treatment of Type II diabetes mellitus.

178. However, physicians have been misled by Defendant to believe that Avandia is superior in its effectiveness and safety to other equally effective and safer alternatives like Actos. As a result of Defendant's widespread misleading marketing and promotion of Avandia's superior safety and effectiveness over safer and equally effective alternative drugs like Actos, many physicians are less inclined to prescribe patients these antidiabetic alternatives.

**2. Avandia Is No Better Than Cheaper Alternatives at Preventing Heart Attacks, Strokes or Deaths**

179. A study published in the *Annals of Internal Medicine* in September 2007 concluded that when compared "with newer, more expensive agents [like Avandia], older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic [blood sugar] control, lipids, and other intermediate endpoints."

180. A June 8, 2009 *Wall Street Journal* article describes a diabetes study sponsored by the National Institutes of Health and several drug companies. The five-year study of 2,368 diabetics was an effort to answer: 1) whether aggressively reopening clogged arteries with stents or bypass surgery work better than inexpensive pills such as beta blockers and other generic heart drugs, and 2) whether diabetes drugs such as Avandia help the body use insulin more efficiently than injecting insulin. The study revealed that aggressive use of expensive diabetes drugs like Avandia performed no better in preventing deaths, heart attacks or strokes than cheaper treatments such as insulin.

181. A February 2010 study published in the journal for the American Diabetes Association, *Diabetes Care*, found that Avandia increases diabetic's heart attack risk by 30% compared with the older diabetes drug sulfonylurea. When

compared with metformin, Avandia increases a diabetic's heart attack risk **by 120%.**

### E. Defendant's Publication Misrepresents Avandia's Safety, Efficacy and Effectiveness and Suppresses Unfavorable Avandia Information

182. Defendant knew or should have known that Avandia was unsafe as compared to other diabetes medications. Despite having knowledge of the increased risk of heart problems related to use of its product, Defendant intentionally, negligently and/or willfully misrepresented the safety and efficacy of Avandia and omitted relevant information showing adverse effects of Avandia, including an increased risk of death or illness due to heart disease or heart attack.

183. Defendant knew or should have known that Plaintiff and the Refund and New York Medical Monitoring Classes would be injured as a result of their misrepresentations and omissions. As a result of Defendant's omissions of, and deliberate misrepresentations related to, critical information regarding the serious health risks associated with Avandia, Plaintiff and the Refund and New York Medical Monitoring Classes:

- were denied the opportunity to limit their exposure to the dangerous side effects of Avandia,
- paid for a drug they would not have otherwise taken and/or,
- paid for more prescriptions of Avandia than they otherwise would have paid for and/or
- paid for Avandia that would have been sold at a lower price had market forces been allowed to operate unfettered by Defendant's violations and/or
- paid for a more effective and/or cheaper alternative medication.

184. From its product launch to the present, Defendant engaged in wide-spread deceptive statements and conduct, and pervasive false and misleading marketing, advertising and promotion of Avandia. Defendant deceived physicians, consumers and others in the medical community regarding the comparative efficacy of Avandia to other medications designed to control Type II diabetes mellitus. Defendant failed to warn – and affirmatively misled – physicians, consumers and others in the medical community regarding Avandia's association with increased risk of heart attacks and heart-related diseases.

185. Defendant also represented that patients could stay on Avandia longer than the older drugs. Additionally, Defendant represented that, unlike the older diabetes drugs, Avandia had the additional benefit of *lowering* diabetics' cardiovascular risks.

186. Despite being on notice of the potential for deadly heart attacks and heart-related diseases, Defendant opted for the bare minima of narrowly-tailored clinical trials, of limited duration, such that little to no side effects were likely to be revealed. Thus, instead of conducting true scientific research in good faith to legitimately test the efficacy and safety of Avandia, Defendant focused on creating studies specifically designed to enhance commercial value.

187. Defendant was required to provide fair and balanced information whenever they engaged in promotional activities. Promotional activities encompass not only written material but all presentations. Defendant knew whenever it was required to provide fair and balanced information, it was required to provide any negative as well as positive information about their drug.

188. In today's health care market, physicians face extreme time constraints in

determining which drugs and treatments are best. Physicians, consumers and third-party payors use a variety of trusted sources including independent studies for such information. Many of these sources are directly controlled or heavily influenced by pharmaceutical manufacturers such as Defendant. All of these sources contain susceptibilities that have been exploited by Defendant and other pharmaceutical manufacturers.

189. Among the tactics employed by Defendant were plans to create studies designed to illustrate Avandia's allegedly superior profile to both (a) placebo and (b) comparable medications designed to control Type II diabetes mellitus while providing funding to engage "key opinion" and "thought" leaders in publication-worthy trials.

190. Upon information and belief, Defendant's scheme was carried out by: making false statements to consumers, physicians and pharmacies concerning the efficacy and safety of Avandia; and training Defendant's employees to conceal negative information regarding Avandia to avoid detection of their activities by Plaintiff and the Refund and the New York Medical Monitoring Classes.

191. Upon information and belief, Defendant sought out, and provided incentives and funding to, doctors and researchers prior to their respective launches to develop deceptive and misleading medical literature for use in marketing.

**1. Misrepresentations in Medical Publications**

192. FDA regulations and industry standards prohibit Defendant from misrepresenting scientific evidence that supports (or fails to support) claims that their respective drug is safe and effective for a specific condition. Thus, anecdotal evidence of a drug's usefulness for a given condition could not be presented as the equivalent of

the findings of a well-designed clinical trial. Failure to comply with these standards violates Defendant's legal duty to provide accurate and non-misleading information.

193. Nevertheless, despite scientifically sound and reliable studies that identify Avandia's adverse effect of increased heart attack and heart-related disease, and the FDA's stringent regulations and recommendations to Defendant regarding the black box labeling of Avandia's adverse side effects, Defendant continued and continues to mislead and deceive consumers by placing full page advertisements in newspapers nationwide.

194. The ads, which appeared in newspapers such as *The New York Times*, *The Washington Post*, *USA Today* and *The Wall Street Journal*, were in the form of a letter to Avandia patients signed by Ronald Krall, GSK's chief medical officer. Therein, Defendant states that they have "conducted an unprecedented number of clinical trials in order to continuously evaluate the safety of Avandia, including its impact on the cardiovasculary system." Defendant claims that the response from the "well-informed" experts and researchers has been "enouraging." Yet despite these "encouraging" studies, the ad warns that Avandia can cause fluid retention, which "can make some heart problems worse or lead to heart failure."

195. Another example of Defendant's attempt to conceal criticisms of Avandia occurred in early on February 21, 2010, when the Editor-in-Chief of the *European Heart Journal* received a letter from Dr. Moncef Slaoui, the chairman of research and development of Defendant, to cease publication of Steven Nissen's editorial on the cardiovascular effects of Avandia. Dr. Slaoui urged the journal not to publish in print an online editorial by Steven Nissen accompanying an analysis on the cardiovascular

effects of rosiglitazone reporting an increased incidence of congestive heart failure in the RECORD trial.

196. Defendant deceived consumers and members of the medical community by overemphasizing controlled and misleading favorable studies, while failing to disclose studies illustrating Avandia's dangerous side effects. Defendant has and continues to expose vulnerable patients with Type II diabetes, including Plaintiff and the Refund and the New York Medical Monitoring Classes, to an increased risk of heart attack and heart-related diseases.

**2. Defendant's Funding for Studies and Payments to Doctors**

197. According to a February 23, 2010 Heart.org article and study presented at the American College of Preventive Medicine Preventive Medicine 2010 annual meeting, an analysis of authors who published reports on Avandia shows that those authors with ties to industry were more likely to conclude that Avandia did not increase myocardial ischemia risk as compared with authors with no industry ties.

198. Among the 202 papers that were evaluated, among authors who concluded Avandia does not increase risk of myocardial ischemia, 91% had financial relationships with antihyperglycemic agent manufacturers and 86% had relationships with Defendant. Among authors of articles representing unfavorable reviews of Avandia, only 25% had financial relationships with antihyperglycemic agent manufacturers and 18% had relationships with Defendant.

http://www.theheart.org/article/1049423.do

199. A June 5, 2007 *The Bulletin* article reveals that Dr. Anne E. Peters, a diabetes expert who operates a clinic for Los Angeles County and who is affiliated with

the University of Southern California medical school, had previously received money from Defendant as a speaker on behalf of Avandia.

200. According to the article, Dr. Peters resigned from that position when she enumerated her concerns about the drug's risks. Dr. Peters said that five years ago, she removed Avandia from the formulary (the list of preferred drugs) maintained by the Los Angeles Clinic. That meant that patients would receive Actos instead of Avandia. "The Avandia people, it was just so surprising, they asked me what I wanted to keep Avandia on the formulary." "Dr. Peters said that she asked the company to establish a database at the clinic that would track the outcomes of patients on both drugs. When she asked for the database, which would have cost several thousand dollars, she said a company representative replied: 'That's all you want? Other doctors ask to go to the Caribbean.'" Dr. Peters said, "They wanted to do everything but approve my request."

201. Further, Avandia's pre-marketing clinical trials were specifically designed to produce positive results and do not support the assertion that the medication is less likely to cause dangerous heart-related diseases. Manufacturers like Defendant fund clinical trials, where the manufacturers create and control the research design. In a 2001 study published in NEJM, researchers found that more than two-thirds of the academic institutions accepted research contracts that prohibit researchers from changing the research design of sponsors like Defendant. Half of the medical centers allowed commercial sponsors to "draft manuscripts reporting the research results, with the investigators' role limited to review and suggestions for revision."

202. In "Ensuring Integrity in Industry-Sponsored Research," published in the March 2010 *Journal of American Medical Association*, editorial authors, Catherine D.

DeAngelis, MD, MPH and Phil B. Fontanarosa, MD, MBA, criticized industry-sponsored drug research for such products as Avandia. Specifically, the authors describes Defendant's dissemination of the Avandia study as "inappropriate conduct surrounding an industry-sponsored clinical trial of rosiglitazone and reveals a situation in which concerns about preserving market share apparently trumped concerns about the potential for causing patient harm."

203. Additionally, in "Setting the RECORD Straight," published in March 2010 *Journal of the American Medical Association*, Steven E. Nissen, MD states that although Defendant's final RECORD article reports that external statistical confirmation was obtained, the extent and depth of these confirmatory analyses still remain uncertain. Furthermore, Nissen explains, as illustrated by the problems with the RECORD trial, absence of independent access to all of the data in the trial may allow physician-scientists to be manipulated by the sponsor, resulting in a manuscript that does not provide the most accurate assessment of the risks and benefits of the therapy. Nissen adds that the requirement of independent outside statistical confirmation of trial results is an essential step and should be universally mandated and would significantly improve the quality of reporting of industry-sponsored clinical trials.

204. According to an April 12, 2010 *New York Times* article, as a response to critics who say the payments to doctors can overly influence how the doctors practice medicine and prescribe drugs like Avandia, pharmaceutical companies like Defendant are now operating databases that disclose payments to doctors who act as consultants or speakers.

205. Defendant's omissions of, and deliberate misrepresentations related to,

critical information regarding the serious health risks associated with Avandia have increased the risk of of disease based on exposure to Avandia and caused financial harm to Plaintiff and the Classes and the sale of Avandia without adequate warning, and based upon false representations regarding its safety, is in violation of New York consumer protection statutes and the common law.

### F. Concealment of Defendant's Conduct and Tolling of Statute of Limitations

206. The applicable statute of limitations regarding the claims of Plaintiff and the Refund and New York Medical Monitoring Classes has been tolled by Defendant's concealment of their unlawful, deceit, as alleged in detail throughout this Complaint.

207. As evidenced by the allegations in this Complaint, Defendant has employed and continues to employ practices and techniques of secrecy in order to avoid detection of, and to conceal, their deceptive and conspiratorial behavior regarding the safety and efficacy of Avandia as well as Avandia's risks associated with heart attacks and heart-related diseases.

208. Defendant successfully concealed from Plaintiff and the Refund and New York Medical Monitoring Classes facts sufficient to excite suspicion of claims against Defendant arising from their deception.

209. Despite taking on the responsibility to reveal this information to the general public, Defendant has kept such information hidden.

210. As such, Plaintiff and the Refund and New York Medical Monitoring Classes were not effectively alerted to the existence and scope of this industry-wide smokescreen and were not on notice of their potential claims until shortly prior to the filing of this Complaint.

211. Plaintiff and the Refund and New York Medical Monitoring Classes could not have acquired such knowledge through the exercise of reasonable diligence.

212. Through their public statements, marketing and advertising, Defendant's self-concealing scheme and affirmative conduct to perpetuate their scheme deprived Plaintiff and the Refund and New York Medical Monitoring Classes members of actual or presumptive knowledge of facts sufficient to put them on notice as to their potential claims.

**G. Injury to Plaintiff and the Class**

*Refund Class Members*

213. Plaintiff and the Refund Class purchased and received Avandia whose benefits and risks – including their serious dangers – had not been properly and accurately assessed and revealed; and that Defendant deliberately ignored, dismissed, and misrepresented evidence regarding the true risks and benefits (or lack thereof) of Avandia – with the intent to deceive and mislead consumers, doctors, and the general public.

214. Plaintiff and the Refund Class purchased and spent money for a lesser-valued Avandia, and in return received drugs that had not been properly investigated and assessed for their safety, risks, and benefits; and the Plaintiff and the Refund received drugs that were not effective and/or safe for conditions and circumstances for which the drugs were promoted in the marketplace.

215. These differences and inferiorities in the drugs that Plaintiff and the Refund Class received, as compared to what they were entitled to receive and reasonably expected to receive, are ascertainable losses.

216. Plaintiff and the Refund Class received Avandia that were different from

and inferior to what they were entitled to receive – not because of any accident or mistake on Defendant's part, but rather as a direct result of Defendant's unlawful deceptive conduct.

217. Relying upon Defendant's promises of superior treatment and better cardiovascular outcomes compared with the older diabetes drugs, Avandia purchasers paid a hefty premium. Data obtained by the Mayo Clinic showed that in October 2007, the average monthly prescription cost for older diabetes drugs like metformin varied from $4 to $100. The cost for Avandia varied from $90 to $220. No justification exists for such a premium.

218. A patient's right to decide on a medication cannot be effectively exercised where a patient is not provided with adequate and accurate information about the risks and benefits of medical treatment. Unless a drug used in medical treatment is adequately tested to ascertain its true safety, risks, and benefits, and those true risks and benefits are accurately provided to consumers who purchase the drugs, the drug's value is compromised and diminished – if not destroyed altogether.

219. Defendant's deceptive and misleading marketing scheme inflated the number of prescriptions of Avandia written and filled during the Class Period. Because Defendant withheld material information about the true effects of Avandia, the prescribing physicians, third-party payors and consumers did not have the knowledge necessary to make informed decisions regarding Avandia prescriptions and formulary placements and Plaintiff and the Refund Class paid higher amounts for Avandia.

220. In order for a drug to be listed on the formulary, it must be assessed by for its clinical safety, efficacy, and cost effectiveness. Additionally, preferred brand

name drugs on these formularies are more likely to be prescribed by a doctor. This system is well known to manufacturers such as GSK, and Defendant knew that any significant negative news regarding Avandia would likely impact formulary decision makers in their evaluations of a drug's formulary status.

221. By directly and falsely promoting Avandia as safe and effective for Type II diabetes and training their sales forces and representatives to avoid alerting the FDA to their activities and to dismiss any safety concerns raised by physicians, Defendant influenced third-party payors to place Avandia high on formularies, doctors to prescribe Avandia, and the Refund Class to pay higher amounts for Avandia.

222. Marketing studies have shown that as the truth about Avandia became known, more insurers, public health care providers, public entities, government payors, and consumers returned to the established diabetes medicines like metformin and sulfonylureas, and Avandia's sales have and will continue to drop.

223. Defendant bilked purchasers, including Plaintiff and the Refund Class, out of hundreds of millions of dollars by making false representations that Avandia was better at lowering blood sugar and could decrease diabetics' cardiovascular risks.

224. Furthermore, Plaintiff and the Refund Class suffered losses when they received drugs that were substantially and materially different from and inferior to what the Plaintiff and the Refund Class were entitled to receive- and that the Plaintiff and the Refund Class received such different and inferior drugs as a result of Defendant's unlawful deceptive conduct.

225. Plaintiff and the Refund Class, unaware of Defendant's scheme, paid a higher purchase price, including higher amounts in co-payments. Although more

effective and safer alternatives are available, Defendant's promotion and marketing of Avandia's safety and effectiveness had been highly successful, resulting in Defendant receiving millions of dollars in pre-tax profits, representing ill-gotten gains to which Defendant was not entitled.

*New York Medical Monitoring Class Members*

226. Plaintiff and the New York Medical Monitoring Class received drugs whose risks and benefits had not been fairly, properly, and adequately disclosed to physicians and consumers.

227. Defendant's conduct caused Plaintiff and the New York Medial Monitoring Class to have an increased risk of contracting a serious latent disease.

228. The medical monitoring Plaintiff and the New York Medical Monitoring Class seek: 1) to create a reasonable and necessary court-supervised medical testing/monitoring program for the pathologic conditions associated with Avandia use both in the past and future. and 2) a court-supervised fund for Plaintiff and the Medical Monitoring Class for the reimbursement of out-of-pocket expenses associated with reasonable and necessary testing/monitoring for pathologic conditions associated with Avandia use, both in the past and future.

229. Plaintiff and the New York Medical Monitoring Class seek to represent Avandia users who have not suffered Avandia-related personal injury which include cardiac ischemia, CAD, and MI, but who are at a "High Risk"of developing cardiovascular ailments.

230. Medical monitoring will give Plaintiff and the New York Medical Monitoring Class an opportunity to survive the harm that Defendant inflicted on them.

## CLASS ACTION ALLEGATIONS

231. Plaintiff brings this suit as a Class action pursuant to Rule 23 of the Federal Rules of Civil Procedure, on behalf of a Refund Class consisting of:

> All consumers who have been prescribed and purchased or paid for part or all of the purchase price other than for resale of the prescription drug Avandia, Avandamet and Avandaryl nationwide since May 25, 1999.

232. Plaintiff also bring this suit as a Class action pursuant to Rule 23(b)(2) of the Federal Rules of Civil Procedure on behalf of New York Medical Monitoring Class.

233. The New York Medical Monitoring Class consists of:

> All persons residing in New York who have been prescribed and ingested Avandia, Avandamet and/or Avandaryl for at least twleve consecutive weeks since May 25, 1999.

234. Excluded from the Classes are employees of Defendant, including its officers or directors, and the Judge to which this case is assigned.

235. Also excluded from the Classes are persons diagnosed with Avandia-related personal injuries which include: cardiac ischemia, CAD, and MI.

236. Plaintiff seeks Class certification under Fed. R. Civ. P. 23(b)(2) as to declaratory and equitable relief sought herein (including medical monitoring), and under Fed. R. Civ. P. 23 as to the damages sought herein.

237. The proposed Refund Class is sufficiently numerous, as thousands of members of the Class were induced to pay for Avandia through Defendant's scheme. The Refund Class members are so numerous and dispersed throughout the United States that joinder of all members is impracticable. The Refund Class is composed of thousands of persons, and the disposition of their claims in a class action will benefit both the parties and the Court. Since its launch in 1999, it is estimated that at least seven

million individuals nationwide received prescriptions for Avandia. Defendant sells millions of doses of Avandia in the United States every year, and thus the Refund Class is sufficiently numerous to make joinder impracticable, if not outright impossible. The Refund Class members can be identified by, *inter alia*, records maintained by Defendant, pharmacies, and PBMs.

238. The proposed New York Medical Monitoring Class is sufficiently numerous, as thousands of New York residents have been prescribed and ingested Avandia, Avandamet and/or Avandaryl for at least twelve weeks since May 25, 1999.

239. Common questions of law and fact exist as to all members of the Refund Class and predominate over any questions affecting solely individual members of the Class. Among the questions of law and fact common to the Refund Class members are:

- whether Avandia was created and designed with defects that increase patients' risk of adverse events;
- whether Defendant knowingly failed to disclose, misrepresent and/or warn of Avandia's defects with the intent that others rely upon such concealment, suppression or ommission;
- whether Defendant misrepresents the safety and efficacy of Avandia, to the financial detriment of the Refund Class;
- whether Defendant's acts and omissions violate, state consumer protection laws;
- whether Defendant makes material misrepresentations of fact, or omits to state material facts to the Refund Class members regarding the the severe heart attacks and heart-related diseases and risks associated with Avandia, which material misrepresentations or omissions operate as a deceit upon the Refund Class;
- whether the Refund Class has been damaged, and if so, the extent of such damages and/or the nature of the equitable relief, compensatory or statutory damages to which the Refund Class is entitled;

- whether Defendant was and is unjustly enriched by its acts and omissions, at the expense of the Refund Class;

240. Common questions of law and fact common to the New York Medical Monitoring Class include:

- whether Defendant misrepresented the safety and efficacy of Avandia;
- whether Avandia was created and designed with defects that increase patients' risk of adverse events;
- whether Defendant committed the intentional, negligent, and wrongful acts described herein;
- whether Avandia increases patients' risk of adverse cardiovascular events;
- whether a monitoring procedure exists that would make early detection of cardiovascular events possible;
- whether this procedure is different from that normally recommended in the absence of Avandia;
- whether this procedure is reasonably necessary according to contemporary scientific principles;
- whether the New York Medical Monitoring Class is entitled to the establishment of a medical monitoring program and for future medical monitoring to detect latent serious diseases associated with Avandia use;

241. Plaintiff's claims are typical of the claims of the members of the Refund Class because Plaintiff and the Refund Class sustained damages arising out of the Defendant's wrongful conduct as detailed herein. Specifically, Plaintiff purchased and/or consumed the hazardous diabetes drug Avandia; expended substantial sums for the purchase of Avandia; asserts claims that are typical of the claims of the entire Refund Class, and will fairly and adequately represent and protect the interest of the Refund Class.

242. Plaintiff's claims are typical of the claims of the New York Medical

Monitoring Class because Plaintiff sustained injury arising out of the Defendant's wrongful conduct as detailed herein. Specifically, Plaintiff was prescribed and consumed Avandia for at least twelve weeks and now faces a heightened risk of disease and requires medical monitoring by reason of their consumption of Avandia. Plaintiff asserts claims that are typical of each member of the New York Medical Monitoring Class and will fairly and adequately represent and protect the interest of the Class.

243. Plaintiff will fairly and adequately protect the interests of the Classes. Plaintiff has retained counsel competent and experienced in Class action lawsuits. Plaintiff has no interests antagonistic to or in conflict with those of the members of the Classes and therefore should be adequate as a representative for the Refund and New York Medical Monitoring Classes.

244. A class action is superior to other available methods for the fair and efficient adjudication of this controversy since joinder of all members of the Classes are impracticable. Furthermore, because the damages suffered by individual members of the Classes may in some instances be relatively small, the expense and burden of individual litigation make it impossible for such Classes'members individually to redress the wrongs done to them. Also, the adjudication of this controversy through a class action will avoid the possibility of inconsistent and possibly conflicting adjudications of the claims asserted herein. There will be no difficulty in the management of this action as a class action.

245. Plaintiff and the Classes have suffered irreparable harm and damages, and continue to suffer losses, thereby allowing these violations of law to proceed without remedy, and allowing Defendant to retain the proceeds of its ill-gotten gains.

## CAUSES OF ACTION

### FIRST CLAIM FOR RELIEF
### (Violation of tile New York General Business Law § 349)

34. Plaintiff Schrank realleges and incorporates by reference each of the factual allegations set forth in this complaint as if set forth herein.

35. Section 349 of the New York's General Business Law states:

> Deceptive acts or practices in the conduct of any business, trade or commerce or in the furnishing of any service in this state are hereby declared unlawful.

36. As set above, the deceptive, acts, practices, and the false representations and omissions made by Defendant to Plaintiff Schrank and the other New York Class members concerning the safety of Avandia were disseminated into New York in the course of conducting their business, trade and services in New York, including but not limited to statements made on the Defendant's website and omissions of material warnings from Avandia's labeling.

37. Defendant's misrepresentations and omissions were likely to mislead reasonable consumers acting reasonably under the circumstances.

38. Defendant's statements, omissions and deceptive scheme, directed at consumers, mislead Plaintiff Schrank and other New York Class members.

39. Defendant's conduct and actions, as described above, constitute deceptive business practices in violation of the GBL.

40. The damages sustained by Plaintiff Schrank and the other New York Class members were a direct and foreseeable result of, and were proximately caused by Defendant's deceptive business practices.

41. As a result of Defendant's actions, Plaintiff Schrank and other Class members have been injured in an amount to be determined at trial.

42. As a result of Defendant's unfair and deceptive trade practices, Plaintiff Schrank seek declaratory and injunctive relief, restitution, actual compensatory damages under the GBL, and attorney's fees.

**SECOND CLAIM FOR RELIEF**
**MEDICAL MONITORING**
**(On Behalf Of The New York Medical Monitoring Class)**

43. Plaintiff realleges and incorporates by reference each of the factual allegations set forth in this complaint as if set forth herein.

44. As a direct and proximate result of Defendant's misrepresentations regarding Avandia's safety, Plaintiff and the New York Medical Monitoring Class have an increased risk of contracting a serious latent disease and will incur (if they have not incurred already) the cost of medical monitoring.

45. This increased risk makes periodic diagnostic medical examinations, beyond those that would be required absent exposure, reasonably necessary. Monitoring and testing procedures exist which make the early detection and treatment of such injuries or disease possible and beneficial.

46. Defendant is liable for all costs associated with a comprehensive, court-supervised monitoring program for members of each putative New York Medical Monitoring Class. This monitoring program, funded by Defendant, will assist members of the putative New York Medical Monitoring Class in the early detection and treatment of Avandia related diseases. Such a program should include the following:

a. a method to notify individual members of each New York Monitoring Class of the risk of Avandia related disease;

b. Provision for the accumulation and analysis of relevant medical and demographic information including, but not limited to, the

results of all appropriate diagnostic tests performed as part of the medical monitoring program;

c. Provision for the creation, maintenance, and operation of a medical registry in which relevant demographic and medical monitoring data is gathered, maintained, and analyzed;

d. Provision for medical research concerning the incidence, prevalence, natural course and history, diagnosis of Avandia related disease;

e. Publication and other dissemination of all such information to relevant health care providers, including physicians; and

f. Provision for the preventative testing and corrective treatment for Avandia related diseases;

47. This proposed medical monitoring plan will help health care providers advise their patients and take steps that substantially reduce the risk of Avandia-related disease.

**THIRD CLAIM FOR RELIEF**
**UNJUST ENRICHMENT**
**(On Behalf of the Refund Class)**

48. Plaintiff realleges and incorporates by reference each of the factual allegations set forth in this complaint as if set forth herein.

49. Defendant has been and continues to be enriched by their deceptive acts and omissions alleged herein for all states wherein the Refund Class' members reside.

50. These deceptive acts and omissions allow Defendant to gain millions of dollars in profits that would not have been gained but for Defendant's deceptive acts and omissions.

51. Plaintiff and Refund Class members and those similarly situated paid and continue to pay Defendant an amount that exceeds the value of the products identified herein as a result of Defendant's acts and omissions.

52. Plaintiff and the Refund Class members suffered damages due to Defendant's acts and omissions as alleged herein.

53. Defendant have and continue to be unjustly enriched as a result of their deceptive acts and omissions.

54. Defendant lack any legal justification for engaging in a course of deceptive acts and omissions as alleged herein at Plaintiff and the Refund Class expense.

55. No other remedy at law can adequately compensate Plaintiff and Refund Class members for the damages occasioned by Defendant's conscious choice to engage in a course of deceptive acts and omissions.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiff and the Refund and New York Medical Monitoring Classes, pray for relief as follows:

1. That this action be certified as a Class action on behalf of the proposed Plaintiff and the Refund Class under Rule 23 and the New York Medical Monitoring Class under Rule 23 and that Plaintiff be designated as the representative of the Class;

2. Establishment of a medical monitoring program;

3. Prejudgment and post judgment interest as provided by law;

4. Compensatory damages as provided by applicable law, including but not limited to refund of all purchase costs on behalf of the Refund Class, as well as out-of-pocket medical monitoring costs that Plaintiff and the New York Medical Monitoring Class have incurred for Avandia;

5. Attorneys' fees, expenses and costs of this action and

6. Such further relief as this court deems necessary, just and proper.

**JURY DEMAND**

Plaintiff hereby demands trial by jury on all issues raised in this Complaint which are triable by jury.

Dated: June 9, 2010 By:

**SCHOENGOLD & SPORN, P.C.**
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*Co-Chairs of PSC Class Action Committee*

**CERTIFICATE OF SERVICE**

I hereby certify that the foregoing Amended Class Action Complaint has been filed by hand with the United States District Court for the Eastern District of Pennsylvania.

I further certify that I am causing a true and correct copy of this document to be served on June 9, 2010, via first class U.S. Mail, postage prepaid upon the following:

Nina M. Gussack, Esq.
Anthony Vale, Esq.
Pepper Hamilton LLP
3000 Two Logan Square
18th and Arch Streets
Philadelphia, PA 19103

JAY P. SALTZMAN